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[54] SYNTHETIC SKIN SUBSTITUTES

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[58] Field of Search 424/78, 447, 78.06, 424/78.32; 525/54.2, 54.22, 54.21; 514/772.5, 777, 780, 781, 782

[56] References Cited

U.S. PATENT DOCUMENTS

3,376,282	4/1968	Schweiger et al.	525/54.2
3,645,939	2/1972	Gaylord	525/54.23
3,969,498	7/1976	Catania et al.	424/28
4,330,441	5/1982	Bohmer et al.	525/54.21
4,393,080	7/1983	Pawelchak et al.	428/355
4,538,603	9/1985	Pawelchak et al.	424/447
4,587,284	5/1986	Luissi et al.	524/17
4,777,046	10/1988	Iwakura et al.	424/447
4,929,577	5/1990	Cornell	424/447

FOREIGN PATENT DOCUMENTS

0130061	1/1985	European Pat. Off. .
0165074	12/1985	European Pat. Off. .
0190814	8/1986	European Pat. Off. .
198344	7/1984	New Zealand .
WO86/02095	4/1986	PCT Int'l Appl. .
1521171	8/1978	United Kingdom .
2036042A	6/1980	United Kingdom .
1594389	1/1981	United Kingdom .
2099704A	12/1982	United Kingdom .

OTHER PUBLICATIONS

Nangia et al "Preclinical Evaluation . . . " Burns (1990) 16(5), pp. 358–367.

Nangia et al "Design of a new . . . " Burns (1989) 15 (6), pp. 385–388.

Nangia et al "Laboratory Evaluation . . . " Burns, (1990) 16(5) pp. 368–372.

Chemical Abstracts, vol. 94 No. 22, Jun. 1 1981, p. 377, Abstract #180641g Wang et al.

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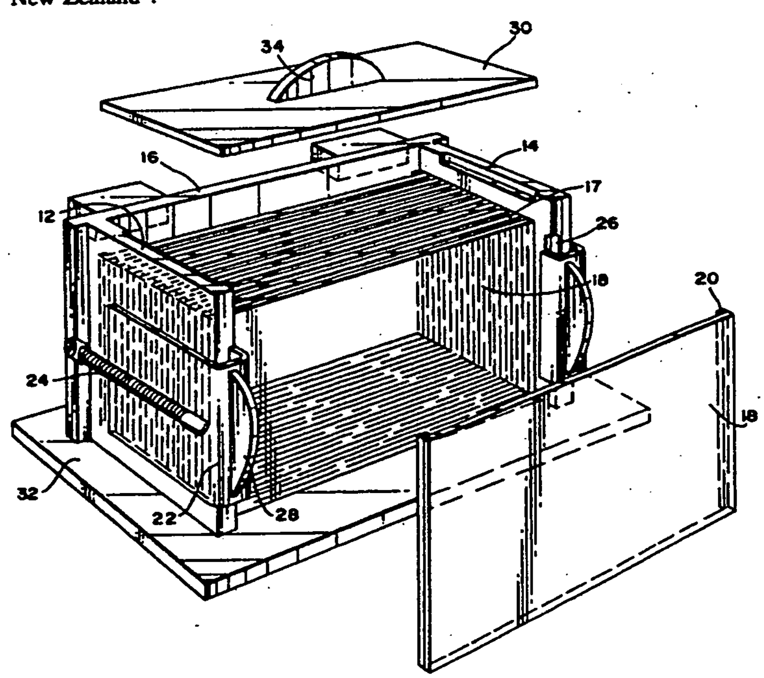
[57] ABSTRACT

Membranes suitable for use as wound dressings and in particular as synthetic skin substitutes are disclosed. The membranes consist of a natural or synthetic polymer, a non-gellable polysaccharide and a cross-linking agent.

The membranes of the invention may contain one or more additional components selected from water-loss control agents, emulsifying agents and plasticizers. An internal reinforcing material may also be provided to supplement the inherent mechanical strength of the membrane.

Methods of forming such membranes are also disclosed.

19 Claims, 1 Drawing Sheet



SYNTHETIC SKIN SUBSTITUTES

BACKGROUND OF THE INVENTION

The outer layer of skin surrounding the body performs an important protective function as a barrier to infection and as a means of regulating the exchange of heat, fluid and gas between the body and external environment. Where the skin is removed or damaged by being abraded, burnt or lacerated, this protective function is diminished. Such areas of damaged skin are therefore conventionally protected by the application of a wound dressing which serves as a skin substitute.

Examples of wound dressings which have been developed are hydrocolloid dressings. UK Patent Number 1471013 and Catania et al U.S. Pat. No. 3,969,498 describe hydrocolloid dressings which are plasma soluble, which form an artificial eschar with the moist elements at the wound site, and which gradually dissolve to release medicaments. These dressings comprise a hydrophilic foam of dextran polymer which can be applied without inunction, is non-irritating to the lesion and is easily removed.

Known hydrocolloid dressings in general, and the Catania dressings in particular, are however subject to a number of drawbacks. The major disadvantages of these dressings are that they disintegrate in the presence of excess fluid at the wound site and that they have little if any control over water loss from the wound. This latter disadvantage is particularly important as excess water loss from a wound will cause an increase in heat loss from the body as a whole, potentially leading to hypermetabolism.

In addition, such hydrocolloid dressings as are known require frequent dressing changes. This is especially true of the Catania dressing due to the dissolution of the dextran polymer at the wound site by the fluid lost through the wound in the exudative stage.

New Zealand Patent Specification Number 198344 discloses a bandage which contains a medicament that is administered topically to the skin of a patient. The bandage disclosed comprises a backing element and a self-adhesive matrix, which matrix in turn comprises a solid phase and a liquid phase with the medicament being molecularly dispersed in the matrix. While the solid phase of the matrix can comprise synthetic polymers and natural gums, no teaching is provided of a synthetic skin substitute which can consist of only a natural or synthetic polymer, a non-gellable polysaccharide and a cross-linking agent.

It is an object of the present invention to go some way towards overcoming the above disadvantages or at least to provide the public with a useful choice.

SUMMARY OF THE INVENTION

Accordingly, in one aspect the present invention can broadly be said to consist in membrane suitable for use as a synthetic skin substitute, said membrane consisting of a natural or synthetic polymer, a non-gellable polysaccharide, and a cross-linking agent.

In one embodiment, the natural or synthetic polymer is a dextran polymer which is cross-linked to the non-gellable polysaccharide by a cross-linking agent.

In a particularly preferred embodiment, the natural or synthetic polymer is polyacrylamide comprising acrylamide monomers cross-linked into a cross-linked mass by said cross-linking agent, the non-gellable polysaccharide being incorporated into said mass.

Conveniently, the non-gellable polysaccharide is a non-gellable galactomannan.

As used herein, the term "non-gellable" means a substance which has no gelling properties in itself, i.e. which does not undergo conformational transition during heating and cooling.

In preferred embodiments, the membrane further includes one or more of a water loss control agent, a plasticizer and an emulsifying agent.

The membrane optionally also includes a reinforcing material, preferably perforated, in order to increase its overall strength. In a further aspect, the invention may be said to consist in a method of preparing a membrane comprising the steps of:

- dispersing a non-gellable polysaccharide in water;
- adding to said dispersion a natural or synthetic monomeric or polymeric material, a cross-linking agent and a cross-linking catalyst, and mixing as appropriate;
- adding the mixture thus formed to a membrane casting apparatus; and
- allowing said mixture to remain in said apparatus under appropriate conditions and for a sufficient time for said membrane to form.

Where the natural or synthetic material is acrylamide, the mixture is maintained in the membrane casting apparatus in the substantial absence of oxygen and at a temperature below 10° C.

Conveniently, said dispersion includes a hydration control agent such as isopropyl alcohol (propan-2-ol) to enhance the formation of a coherent close knit mass of non-gellable polysaccharide.

It will be appreciated that the monomeric or polymeric material, the cross-linking agent and the cross-linking catalyst can be added to the dispersion together or separately.

Conveniently, the method includes the preliminary step of forming a solution comprising the monomeric or polymeric material, the cross-linking agent and the cross-linking catalyst and adding the solution to the dispersion. Alternatively, the method may include the steps of forming a solution comprising the monomeric or polymeric material and the cross-linking agent, adding the solution to the dispersion and conducting a first mixing step, then adding the cross-linking catalyst and conducting a second mixing step prior to adding the mixture to the membrane casting apparatus.

Where the membrane is to include a perforated reinforcing material, the material is appropriately positioned within the casting apparatus prior to the addition of the mixture.

Also described herein is a membrane casting apparatus including:

- first and second framing members, said framing members being positionable opposite and substantially parallel to each other;
- a plurality of partitioning members, said partitioning members being positionable spaced apart between said framing members and substantially parallel to each other such that a separate open-ended compartment is formed between the framing members and adjacent partitioning members;
- means capable of spacing said partitioning members apart;
- means capable of retaining said partitioning members in position;

Where the membrane is to be used as a skin substitute in an area which requires a particular degree of elasticity, a plasticiser such as glycerol may be incorporated into the composition as an additional component. Glycerol may be substituted by other known plasticisers such as sorbitol, propylene glycols, PEG-400, PEG-75-lanolin oil, diethylene glycol, acetylated lanolin or mixtures thereof.

The membrane optionally further includes a reinforcing material to enhance the strength of the product. The reinforcing material is preferably in the form of a sheet or net of material, the shape and dimensions of which correspond substantially to those of the membrane to be coextensive therewith. It is further preferred that the material be incorporated having a membrane layer on either side thereof. In this embodiment, the reinforcing material is perforated to allow both sides of the membrane to bond together through the perforations and to allow fluid communication between both sides of the membrane. This latter feature is important to maximise the absorptive capacity of the membrane for wound exudate.

The presently preferred reinforcing material is a perforated polyester material. However, any of those reinforcing materials known in the art which would be suitable for the purpose could be used. By way of illustration, polyethylene, polypropylene, PVC, polystyrene, PTFE, cellusiose derivatives, polybutadiene, polylactide, polyurethane, polypeptides, poly (E-caprolactone), nylon, keratin, collagen, chitin, chitosen, Styrene-butadiene copolymers and derivatives thereof can also be used, either alone or in a mixture.

The membranes according to the present invention may be prepared in accordance with the following process.

The first step of the process comprises the formation of a dispersion of the non-gellable polysaccharide component of the membrane in water. This dispersion may advantageously also include a hydration control agent for the polysaccharide to enhance the formation of a coherent, close-knit mass. In addition, where such a hydration control agent is present, the polysaccharide macromolecule can be used at higher concentrations. An example of suitable hydration control agent is isopropyl alcohol (propan-2-ol).

The second step of the process involves the addition of the remaining components of the membrane (the monomeric or polymeric material and the cross-linking agent) together with a cross-linking catalyst to the dispersion. The cross-linking catalyst is added to catalyse the cross-linking reaction involved in the formation of the membrane. Examples of suitable catalysts are NNN'N'-tetramethylene diamine and ammonium persulfate.

All of the components are then mixed together and homogenized before being poured into a membrane casting apparatus. Although it is preferred that the membrane casting apparatus is that described hereinafter as an aspect of the invention, this is not critical. Instead, the casting apparatus may be any of those known in the art suitable for this purpose. This is particularly the case where the membrane being formed includes dextran which does not require the controlled polymerisation conditions set out below necessary to form the polyacrylamide membrane.

Where the membrane being formed includes acrylamide monomers cross-linked to form polyacrylamide, the mixture is then maintained in the absence of oxygen at a temperature of less than 10° C. for a period of time sufficient for the membrane to form. Conveniently, the mixture is maintained at a temperature between 4° and 10° C. during the polymerisation process.

In contrast, where the membrane to be formed includes dextran the polymerisation mixture is maintained at room temperature and is open to air.

The monomeric or polymeric material, the cross-linking agent and the cross-linking catalyst can be added to the dispersion either together or separately. Where each of the above components are to be added to the dispersion together, a solution containing them is formed which is then added to the dispersion. The solution and the dispersion are then mixed to provide the mixture to be added to the membrane casting apparatus. In other embodiments of the method, the monomeric or polymeric material and the cross-linking agent are added to the dispersion separately from the cross-linking catalyst. In this embodiment, a solution comprising the monomeric or polymeric material and the cross-linking agent is added to the dispersion and a first mixing step conducted. The cross-linking catalyst is then added, a second mixing step conducted, and the resulting mixture poured into the membrane casting apparatus.

Where the membrane to be formed is also to include a water loss control agent and/or an emulsifying agent as components, these are also added to the dispersion prior to the mixing step. Again, these preferred components can be added either separately or together with the other components.

Where the membrane is to include a reinforcing material, this material is positioned with each compartment of the membrane casting apparatus prior to the addition of the polymerisation mixture.

If desires, the incorporation of the plasticiser into the membrane is achieved by immersing the membrane formed as above into an aqueous solution of the plasticiser. The concentration of the plasticiser and duration of the membrane immersion in the aqueous solution will depend on the degree of elasticity desired for that particular membrane.

The present invention will be more clearly understood by having reference to the following non-limiting examples.

EXAMPLE 1

Formation of a membrane including acrylamide

0.8 g of purified guar-gum (molecular weight of 2.2 million) was dispersed in 20 ml of a mixture containing 2 ml of isopropyl alcohol (propan-2-ol) and 18 ml distilled water to form a dispersion. 7 g of monomeric acrylamide and 160 mg of NN'-methylenebisacrylamide were dissolved in 20 ml of distilled water to form a solution. 0.8 g of L-α-phosphatidylcholine was solubilised in 20 ml of distilled water using 50 mg of sodium lauryl sulfate using an ultrasonic probe to form a second dispersion.

The solution and the second dispersion were then added to the first dispersion and homogenised for about five minutes. 100 μl of NNN'N'-tetramethylene-diamine and 100 mg of ammonium persulfate were then added to and mixed into the mixture.

The resulting mixture was then poured into a membrane casting apparatus as is described below and allowed to cross-link in the absence of air and at a temperature of from 4° to 10° C. for period of time sufficient to allow the membrane to form.

elements allows the reinforcing material to be fixed in a position within each compartment by being held between the abutting suraces of the respective spacing elements.

The preferred apparatus also includes paired positioning means which bias the partitioning member 18 toward backing member 16. As shown each positioning means comprises a portion 22 for contacting the outermost partitioning member and a spring 24 attached at one end to the contact portion 22 and at the other end to backing member 16. At the end of framing members 12 and 14 remote from backing member 16 there is provided a ledge 26 onto which contact portion 22 can be positioned out of engagement with the partitioning members 18 to allow for easy removal of the partitioning members. A gripping element 28 is also attached to each contact portion 22 to facilitate the movement of the contact portion to its rest postion on ledge 26.

The apparatus further includes closure members in the form of a lid 30 and a base 32 which serve to cover the top and bottom openings of each compartment 17. Lid 30 is also provided with a gripping element 34 to allow easy removal.

In operation, the components of the apparatus as shown are assembled. Where the membrane is to include a reinforcing material, this is positioned in each compartment 17 and held in position between the spacing elements. The mixture formed in accordance with the process of the invention is added to the compartments 17 and the lid 30 positioned to close each compartment.

Following the formation of the membrane, the lid 30 is removed, the contact portion 22 is moved out of engagement with the outermost partitioning member and the partitioning members 18 removed. The formed membranes are then separated from the partitioning members for further treatment.

The membranes of the invention of the preferred polyacrylamide formulation have been subjected to a number of tests. The results of these tests are as follows.

The polyacrylamide membranes of the present invention formed as above are permeable to water vapour. The water vapour permeation transmission was determined on excised skin wounds of rats covered with a membrane. An EVAPORIMETER (Servomed AB) was used to find the water vapour transmission. The data obtained shows that the permeability of membrane is in the range of 1400–2500 grams/m^2/24 hours. The membranes therefore have water vapour transport characteristics sufficient to keep the underlying tissues moist without fluid pooling or dehydration, both of which conditions retard wound healing.

The oxygen permeability of the membrane was measured by using a specially designed oxygen permeability cell using an oxygen electrode. The data obtained shows that the dissolved oxygen permeability of the membrane is int he range of 1.4–2.40×10^{-9} [cm^3.(STP).cm/cm.^{2}sec.cm.Hg]. Therefore the membrane is highly permeable to oxygen which will promote wound healing.

The polyacrylamide membranes of the present invention also have a high absorption capacity for exudate and tissue secretions at the wound site. When the membrane was immersed in distilled water at ambient temperature of 22° C., the rate of water absorption was 900% in 24 hours, without losing durability. The present membranes are therefore highly suitable for use in treating wounds which produce large amounts of exudate.

The membranes of the present invention are also elastic, self-supporting and flexible. Tensile properties of the polyacrylamide membranes were studied according to ASTM D882-81, 1981 at 65% relative humidity (21° C.). The elongation at the breaking point of the membrane is 400–750%, with a tensile strength of 2–3 MPa and an initial modulus of 0.5–0.9 MPa. It will be clear to those persons skilled in the art that the elasticity of the membrane can be adjusted by altering the concentration of plasticizer and components of the membrane, allowing the membrane to be stretched over joints without causing a shear stress that will break the adherence between the dressing and the wound surface.

In order to demonstrate the effectiveness of the membrane according to the invention as a skin substitute, the following clinical experiments were performed.

EXPERIMENT 1

The objective of this experiment was to evaluate the effectiveness of the membrane of the invention (SSS) in the management of excised skin wound in the rats. Its effectiveness has been compared with two marketed products Geliperm Dry (Geistlich Pharma) and Bioclusive (Johnson and Johnson) used for the same purpose.

Experimentation

Sprague-Dawley rats weighing 200–250 gms were anaesthetised by an intraperitoneal injection of pentobarbital and shaved with a clipper. A 4×4 cm area, about 15% of the rat skin, was excised from the dorsal surface with a Reese Drum Dermatome. Histological studies of the skin sections revealed that it was a split thickness injury covering epidermis and most of the dermis. A total of 20 rats were used in the study. Three groups comprising of five randomly selected rats were applied with SSS or Bioclusive or Geliperm Dry and the remaining five rats used as controls with air exposure. In the case of SSS and Geliperm, the membranes were fixed to the wound site with the help of an adhesive tape.

All the animals were observed daily for the evaporative water loss through the membranes, appearance of the wound and the rate of healing.

Results

SSS adhered uniformly onto the wound surface and absorbed exudate from the wound. SSS also appeared to stop bleeding at the wound site and acted as a haemostatic agent. Bioclusive, due to its thin and flexible nature also conformed well to the wound surface. However, it did not absorb the exudate from the wound. Geliperm Dry did not adhere uniformly to the wound side and air pockets were observed between the wound and the dressing. In addition, the membrane showed mimimal exudate absorbing capacity.

When the animals were inspected on day 3 post operation, all rats with Bioclusive showed evidence of pooling of excess exudate and maceration of the wound. The exudate was shown to be contaminated with *Pseudomonas seruginosa* and *Staphylococcus aureus*. Rats with Geliperm Dry showed no adherence to the wound. As it did not protect the wound from desiccation, a thick crust formation on the wound surface was observed. Animals treated with SSS showed uniform adherence to the wound, without fluid accumulation and with no infection. On day 8 post-operation the animals were

membrane as a delivery system for topical therapy as compared to those dressings known. By way of example the serated dextran dry foam described by Catania et al in U.S. Pat. No. 3,969,498 dissolves in water in thirty seconds or less, thus releasing the incorporated drug immediately at the open wound site. In contrast, the membranes of the present invention release the drug slowly over a prolonged period of time, thus eliminating the hazards of dose dumping.

The membranes are also impermeable to microorganisms and accordingly assists wound healing by keeping the wound clean.

Where the membranes incorporate a perforated reinforcing material, the overall strength of the membranes is increased, together with their conformability. This latter feature in particular allows the membranes to be moulded to fit the surface to be covered.

Other advantages of the membranes reside in their transparent nature, allowing wound inspection without removal, and in that they are non-toxic, non-allergenic, antiseptic, easy to apply and remove without inunction, allow gaseous exchange, provide thermal insulation for the wound and are relatively inexpensive.

Thus, in accordance with the present invention there are provided membranes particularly suitable for use as synthetic skin substitutes. To those persons skilled in the art the invention will have obvious utility as a short and long term skin substitute for second and third degree burns, excised wounds, donor sites, ulcers and dermal abrasions.

It will be appreciated by those persons skilled in the art that the above description is provided by way of example only and that it should not be construed as a limitation on the scope of invention to which the applicants are entitled.

What is claimed is:

1. A membrane suitable for use as a synthetic skin substitute consisting essentially of a polyacrylamide network and a non-gellable polysaccharide dispersed evenly throughout said network, wherein said polymeric polyacrylamide network comprises acrylamide monomers cross-linked together by a cross-linking agent and wherein the membrane has a water absorptive capacity greater than of a membrane which includes an amount of a gellable polysaccharide in substitution for the same amount of non-gellable polysaccharide, but which is otherwise the same.

2. A membrane according to claim 1, wherein the non-gellable polysaccharide is a non-gellable galactomannan.

3. A membrane according to claim 2, wherein the non-gellable galactomannan is guar gum.

4. A membrane according to claim 2, wherein the non-gellable galactomannan is selected from honey locust bean gum, white clover bean gum and carob locust bean gum.

5. A membrane according to claim 1, wherein the cross-linking agent is NN'-methylenebisacrylamide.

6. A membrane according to claim 1, wherein the cross-linking gent is selected from bisacrylylcystamine and diallyltartar diamide.

7. A membrane according to claim 1, further including a water-loss control agent.

8. A membrane according to claim 7, wherein the water loss control agent is a phospholipid.

9. A membrane according to claim 8, wherein the phospholipid is L-α-phosphatidylcholine.

10. A membrane according to claim 8, wherein the phospholipid is present in the form of lipid vesicle liposomes which contain an active agent for delivery to the surface upon which the membrane is disposed in use.

11. A membrane according to claim 10, wherein the active agent for delivery is an antimicrobial compound, a germicide, a steroid, an anaesthetic, a chemotactic agent, an angiogenic agent or an epidermal growth factor.

12. A membrane according to claim 1, further including an emulsifying agent.

13. A membrane according to claim 12, wherein the emulsifying agent is sodium lauryl sulphate.

14. A membrane according to claim 1, further including a plasticizer.

15. A membrane according to claim 14, wherein the plasticizer is glycerol, sorbitol, a propylene glycol, PEG-400, PEG-75-lanolin oil, diethylene glycol, acetylated lanolin or a mixture thereof.

16. A membrane according to claim 1, further including a reinforcing material.

17. A membrane according to claim 16, wherein the reinforcing material is a plastics net or mesh, or a perforated sheet of plastics material.

18. A membrane according to claim 17, wherein the reinforcing material comprises a perforated polyester sheet.

19. A method of treating burns, donor sites, excised wounds, ulcers or dermal abrasions of a non-human patient comprising applying a membrane as claimed in claim 1 to said burn, donor site, wound, ulcer or abrasion.

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